AN ONGOING OPEN-LABEL PHASE I/IIA STUDY OF THE SAFETY AND EFFICACY OF MELFLUFEN AND DEXAMETHASONE COMBINATION FOR PATIENTS WITH RELAPSED AND RELAPSED-REFRACTORY MULTIPLE MYELOMA

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Background:

Melflufen (L-melphalanyl-*p*-L-fluorophenylalanine ethyl ester hydrochloride), is a targeted analogue of melphalan. The mechanism of action is targeted alkylation of tumor cell DNA. Treatment with melflufen results in efficient intracellular trapping of melphalan, preferentially in tumor cells. Transport of melflufen into cells is rapid since it is lipophilic. Once inside the cytoplasm, peptidases that often are overexpressed in malignant cells, will rapidly cleave melflufen and thereby release melphalan. Melphalan is hydrophilic and hence transport out of cells is slow.

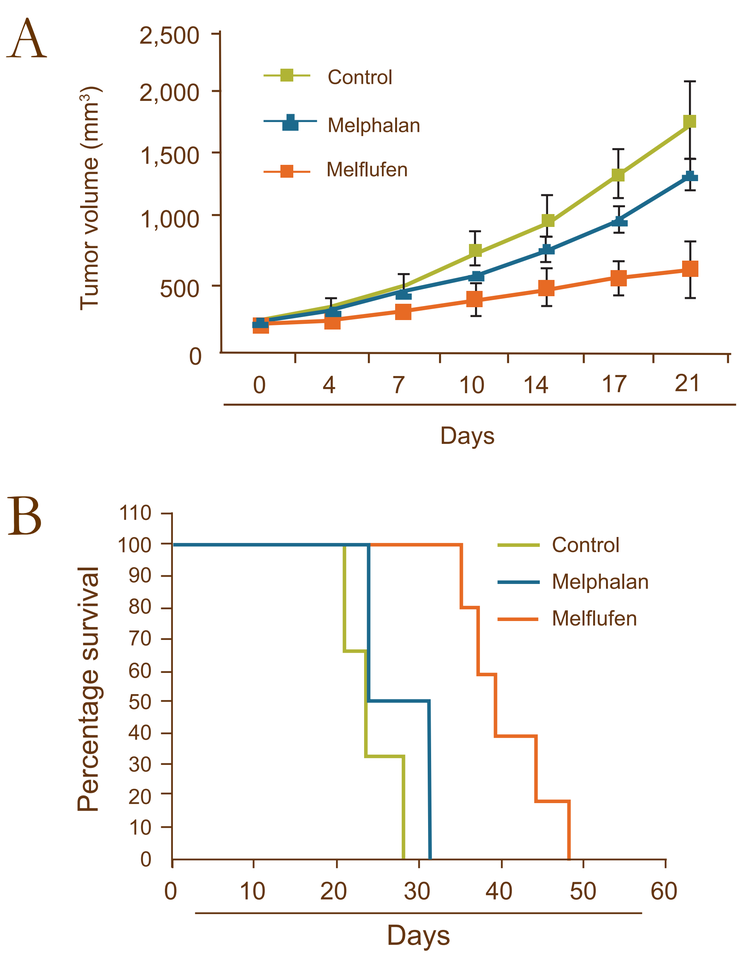
Treatment of myeloma cells with melflufen results in a more than 20-fold higher intracellular concentration of melphalan, compared with direct treatment with melphalan, resulting in a proportional increase in cytotoxic potency[1].

When studied in cultures of human tumor cells representing approximately 20 different human cancers, including multiple myeloma, melflufen showed 50 to 100 fold higher cytotoxicity and tumor growth suppression compared with that of melphalan[2].

In efficacy studies conducted in mice and rats, superior antitumor activity of melflufen over melphalan was observed with comparable toxicity (Figure 1).

In a first-in-man study, a total of 45 patients with advanced solid tumors received a total of 141 cycles of melflufen at doses of 25-130 mg, with a safety profile quantitatively and qualitatively similar to that of melphalan. The dose limiting toxicity was bone marrow suppression, mainly reversible thrombocytopenia, and the recommended Phase II dose was established at 50 mg.

Figure 1. Pre-clinically meflufen is superior to melphalan



A. Tumor-bearing mice (human plasmacytoma xenograft model) were intravenously treated with vehicle, melflufen (2mg/kg) or equimolar dose of melphalan.

B. Survival in mice receiving melflufen vs melphalan ($p<0.05$).

Aims:

To study the safety and efficacy of treatment with melflufen and dexamethasone (dex) in combination in patients with relapsed refractory multiple myeloma (RRMM).

Methods:

This is an ongoing open-label, phase I/IIa, multicenter trial of melflufen plus dex, currently enrolling patients with RRMM (NCT01897714).

Phase I follows the standard 3 + 3 modified Fibonacci design with 3 to 6 patients in each cohort, depending on the dose limiting toxicity (DLT) observed following one cycle of therapy. Up to 4 dose levels will be tested; IV melflufen at 15 mg, 25 mg, 40 mg and 55 mg, given on day 1, with a fixed dose of dex 40 mg PO or IV on days 1, 8 and 15 of each 21 day cycle. An additional 20 patients will be treated at the maximum tolerated dose (MTD) in the Phase IIa part of the study.

The primary objectives are to determine the MTD in Phase I and the objective response rate in Phase IIa.

Adult patients with measureable disease, ≥ 2 lines of prior therapy, life expectancy ≥ 6 months, ECOG ≤ 2, absolute neutrophil count ≥ 1.0 x 10^9/L, pl atelet count ≥ 75 x 10^9/L, hemoglobin ≥ 8.0 g/dl, total bilirubin ≤ 1.5 x upper limit of normal (ULN), estimated creatinine clearance ≥ 45 ml/min, serum creatinine ≤ 2.5 mg/dL and AST/ALT ≤ 3.0 x ULN are eligible for the study.

All patients are required to provide signed informed consent.

Data cut off for the poster was 2 May 2014.

Results - Baseline Characteristics:

Parameter Median (range)	15mg N=4	25mg N=7	40mg N=3
Age	66 (50-77)	68 (58-82)	60 (54-69)
Gender	2F + 2M	4F + 3M	1F + 2M
Years since diagnosis	7 (3-13)	6 (1-10)	10 (4-15)
Number of prior lines	4.8 (3-7)	5.7 (2-10)	3.7 (3-4)
Prior melphalan exposure	2 yes 2 no	3 yes 4 no	2 yes 1 no
Prior Proteazome Inhibitors or IMiDs	All patients had received both classes in previous lines of therapy		

Results – Safety:

- No DLTs seen in 15 mg, 25 mg or 40 mg cohorts
- 39 cycles (range 1-10) of melflufen given to 14 patients
- 29 related AEs reported in 9 patients
- 6 related grade 3-4 AEs reported in 4 patients

Total number of possibly related AEs = 29		
Thrombocytopenia	6	21%
Anemia	3	10%
Neutropenia	3	10%
Fatigue	3	10%
Constipation	2	7%
Nausea	2	7%
Febrile neutropenia	1	3%
Infection - bacteremia	1	3%
Leukopenia	1	3%
Lymphopenia	1	3%
Mucositis	1	3%
Muscle spasm	1	3%
Paresthesia	1	3%
Peteckia lower limb	1	3%
Pneumonia	1	3%
Thromboembolic event (DVT)	1	3%

Grade 3/4 possibly related AEs	15mg (19 cycles)	25mg (14 cycles)	40 mg (6 cycles)
Thrombocytopenia (G3)	1*		
Pneumonia (G3)	1*		
Febrile neutropenia (G4)	1*		
Neutropenia (G3)		1	
Lymphopenia (G3)		1	
Infection – bacteremia (G3)		1	

* reported in the same patient

Results – Efficacy

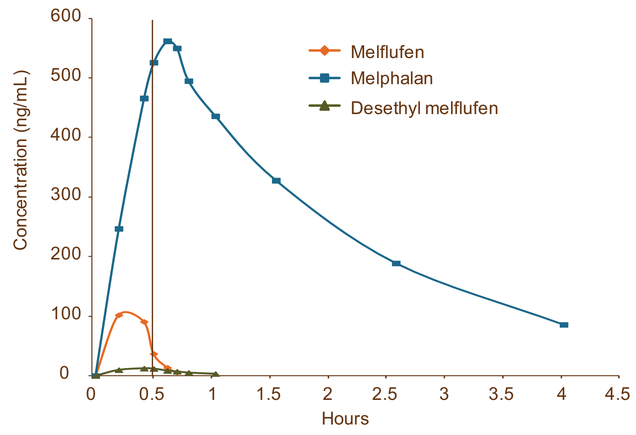
In the 15 mg and 25 mg cohorts, Stable Disease was reported as best response, with a total of 19 cycles given in 4 patients in the 15 mg cohort and 14 cycles given in 7 patients in the 25 mg cohort.

One patient at the 15 mg cohort has completed 10 cycles of therapy and remains in stable disease. The dose was increased to 25 mg at cycle 10.

One patient in the 40 mg cohort achieved a minor response after one cycle coinciding with data cut off.

No further efficacy results were available at the time of data cut off.

Figure 2. Melflufen pharmacokinetics of one patient treated with 25 mg of melflufen



The vertical line shows the time at which the infusion ended. It highlights the decrease in melflufen concentrations during the infusion and the delay in reaching peak concentration for melphalan after the end of the infusion.

Results - Pharmacokinetics:

Pharmacokinetics were evaluated in three patients at one center (Figure 2).

The conversion of melflufen to melphalan was rapid and complete.

The concentration of the other metabolite (des-ethyl-melflufen) was low.

The delay in the peak concentration of melphalan supports that melphalan is primarily formed from melflufen in peripheral tissue and then redistributed to blood.

The systemic exposure (AUC) in blood of melphalan following melflufen administration is similar to that found following equimolar administration of melphalan.

Conclusions:

- No dose limiting toxicity was observed at dose levels 15, 25 and 40 mg of melflufen
- One MR achieved at the 40 mg dose level within one cycle of therapy just prior to data cut off
- Melflufen is rapidly and completely converted to melphalan in peripheral tissues
- Dose escalation cohort 4 (55 mg) is currently ongoing

References

1. D. Chauhan et al., Clin Cancer Res 2013; 10:3019-3031; *In Vitro* and *In Vivo* Antitumor Activity of a Novel Alkylating Agent, Melphalan-Flufenamide, against Multiple Myeloma Cells
2. M. Wickström et al., Invest New Drugs (2008) 26:195–204; The novel alkylating prodrug J1: diagnosis directed activity profile ex vivo and combination analyses *in vitro*

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